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Trends and centre-to-centre variability in survival rates of very preterm infants (<32 weeks) over a 10-year-period in Switzerland

Berger, Thomas M ; Steurer, Martina A ; Woerner, Andreas ; Meyer-Schiffer, Philipp ; Adams, Mark

Abstract: **BACKGROUND:** The publication of Swiss guidelines for the care of infants at the limit of viability (22-25 completed weeks) was followed by increased survival rates in the more mature infants (25 completed weeks). At the same time, considerable centre-to-centre (CTC) differences were noted. **OBJECTIVES:** To examine the trend of survival rates of borderline viable infants over a 10-year-period and to further explore CTC differences. **DESIGN:** Population-based, retrospective cohort study. **SETTING:** All nine level III neonatal intensive care units (NICUs) and affiliated paediatric hospitals in Switzerland. **PATIENTS:** 6532 preterm infants with a gestational age (GA) <32 weeks born alive between 1 January 2000 and 31 December 2009. **MAIN OUTCOME MEASURES:** Trends of GA-specific delivery room and NICU mortality rates and survival rates to hospital discharge were assessed. For CTC comparisons, centre-specific risk-adjusted ORs for survival were calculated in three GA groups: A: 23 0/7 to 25 6/7 weeks (n=976), B: 26 0/7 to 28 6/7 weeks (n=1943) and C: 29 0/7 to 31 6/7 weeks (n=3399). **RESULTS:** Survival rates of infants with a GA of 25 completed weeks which had improved from 42% in 2000/2001 to 60% in 2003/2004 remained unchanged at 63% over the next 5 years (2005-2009). Statistically significant CTC differences have persisted and are not restricted to borderline viable infants. **CONCLUSIONS:** In Switzerland, survival rates of infants born at the limit of viability have remained unchanged over the second half of the current decade. Risk-adjusted CTC outcome variability cannot be explained by differences in baseline demographics or centre case loads.

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Trends and centre-to-centre variability in survival rates of very preterm infants (<32 weeks) over a 10-year-period in Switzerland

Thomas M Berger,¹ Martina A Steurer,² Andreas Woerner,³ Philipp Meyer-Schiffer,⁴ Mark Adams⁴, for the Swiss Neonatal Network

¹Neonatal and Paediatric Intensive Care Unit, Kinderspital Luzern, Luzern, Switzerland

²Division of Pediatric Critical Care, University of California Medical Center, San Francisco, California, USA

³Neonatal Intensive Care Unit, Universitätskinderklinik, Bern, Switzerland

⁴Department of Neonatology, Universitätsspital Zürich, Zurich, Switzerland

Correspondence to

Dr Thomas M Berger, Neonatal and Paediatric Intensive Care Unit, Kinderspital Luzern, Spitalstrasse, CH-6000 Luzern 16, Switzerland; thomas.berger@luks.ch

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ABSTRACT

Background The publication of Swiss guidelines for the care of infants at the limit of viability (22–25 completed weeks) was followed by increased survival rates in the more mature infants (25 completed weeks). At the same time, considerable centre-to-centre (CTC) differences were noted.

Objectives To examine the trend of survival rates of borderline viable infants over a 10-year-period and to further explore CTC differences.

Design Population-based, retrospective cohort study.

Setting All nine level III neonatal intensive care units (NICUs) and affiliated paediatric hospitals in Switzerland.

Patients 6532 preterm infants with a gestational age (GA) <32 weeks born alive between 1 January 2000 and 31 December 2009.

Main outcome measures Trends of GA-specific delivery room and NICU mortality rates and survival rates to hospital discharge were assessed. For CTC comparisons, centre-specific risk-adjusted ORs for survival were calculated in three GA groups: A: 23 0/7 to 25 6/7 weeks (n=976), B: 26 0/7 to 28 6/7 weeks (n=1943) and C: 29 0/7 to 31 6/7 weeks (n=3399).

Results Survival rates of infants with a GA of 25 completed weeks which had improved from 42% in 2000/2001 to 60% in 2003/2004 remained unchanged at 63% over the next 5 years (2005–2009). Statistically significant CTC differences have persisted and are not restricted to borderline viable infants.

Conclusions In Switzerland, survival rates of infants born at the limit of viability have remained unchanged over the second half of the current decade. Risk-adjusted CTC outcome variability cannot be explained by differences in baseline demographics or centre case loads.

Over the past 20 years, survival rates of infants born at the limit of viability have improved substantially and, in some countries, have reached between 51% and 67% and 67% and 81% for preterm infants with a gestational age (GA) of 24 and 25 completed weeks, respectively.^{1–5} At the same time, rates of neurosensory impairment are still a major concern, and between 23% and 40% of survivors at 24 completed weeks have been reported to be profoundly impaired (psychomotor developmental index (PDI) and/or motor developmental index (MDI) <50 or IQ <55, adult assistance is required to move, blindness, deafness). This rate drops below 25% in survivors at 25 completed weeks.^{5–7}

What is already known on this topic

- ▶ Following the publication of Swiss recommendations for the care of borderline viable infants survival rates of infants at 25 completed weeks improved.
- ▶ In Switzerland, considerable centre-to-centre differences in survival rates of borderline viable infants have been noted in earlier studies.

What this study adds

- ▶ Since 2004, survival of live born extremely preterm infants with a GA of 24 and 25 completed weeks has not changed significantly.
- ▶ In Switzerland, considerable centre-to-centre differences in survival rates continue to persist and extend beyond the borderline viable preterm infant population.

Many national perinatal societies have published recommendations to support ethical decision making in the care of borderline viable infants.^{8–15} The publication of the Swiss recommendations for the care of infants born at the limit of viability (22–25 completed weeks) in the year 2002 was followed by an increase in survival rates in the more mature extremely preterm infants (25 completed weeks) without increasing the rate of short-term complications. At the same time, significant centre-to-centre (CTC) differences in survival rates persisted despite the availability of national guidelines.¹⁶ Because there were no significant differences in baseline population demographics between centres, it seemed likely that the observed differences were at least in part due to variations in ethical decision making.¹⁶ In addition, other factors that have been linked to outcome, such as unit size (ie, case load) and organisational characteristics (eg, referral patterns, proportion of outborn infants and staffing) may also have played a role.

In this present study, we had two aims: first, we wanted to assess whether survival rates of extremely preterm infants have continued to improve in Switzerland. Second, we wanted to



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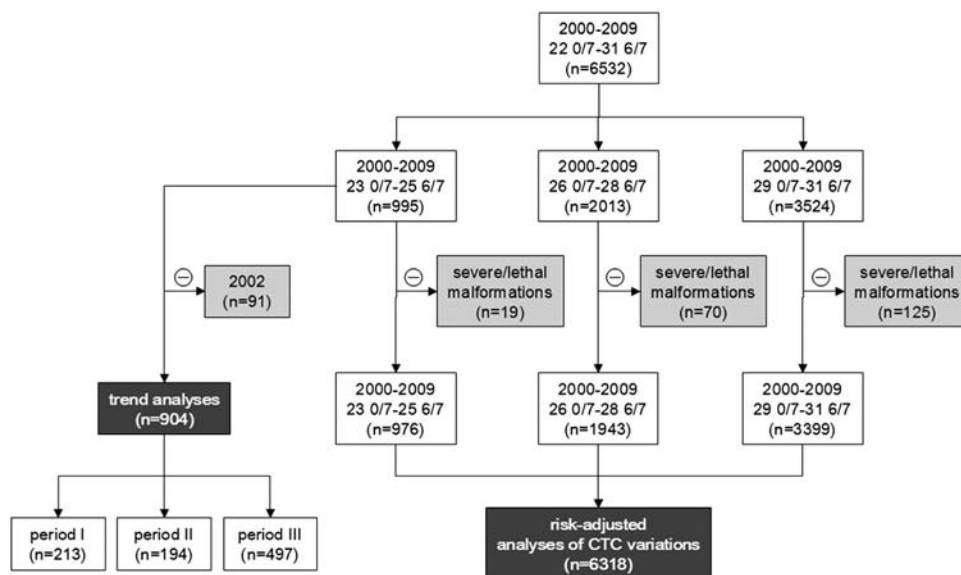


Figure 1 Study population. For trend analyses, patients born in 2002 (year of the publication of the Swiss recommendations for the care of infants born at the limit of viability) were excluded and survival rates in period I: 2000/2001, period II: 2003/2004 and period III: 2005–2009 were compared; for analyses of centre-to-centre variations, patients with severe/lethal malformations were excluded.

explore CTC outcome variability in more detail by extending the study population to a longer time period (10 years) and to more mature preterm infants (GA up to 31 6/7 weeks). We hypothesised that CTC outcome variability would diminish with advancing GA if differences in ethical decision making were the main reasons for significantly different survival rates of borderline viable infants in Switzerland.

Methods

The well-established Swiss Minimal Neonatal Data Set was used to analyse data on all live born preterm infants with a GA between 23 0/7 and 31 6/7 weeks (ie, 23–31 completed weeks) over a 10-year period between 1 January 2000 and 31 December 2009. All nine neonatal intensive care units (NICUs) and affiliated paediatric hospitals that care for extremely preterm infants in Switzerland participated in this study. Data were collected prospectively through a computerised questionnaire distributed to collaborators from each centre. GA was calculated based on obstetric expected due dates if the mother's dates were consistent with ultrasound examinations during the first trimester of pregnancy. Across all participating centres, GA was defined according to the *International Classification of Disease*¹⁷ as the postmenstrual age in weeks and days. The time period between 25 weeks and 0 days and 25 weeks and 6 days, for example, is termed 25 completed weeks of gestation; the fetus has completed 25 weeks and is in the 26th week of gestation. Completed data forms were sent to a central site (Department of Neonatology, University Women's Hospital, Zurich, Switzerland) where they were collected and evaluated. To verify that the outcome of all live born infants at the limit of viability were completely ascertained, including those who had died in the delivery room, the birthing log books or electronic databases at all participating hospitals were reviewed by one of our group.

To follow the trend of survival in extremely preterm infants (GA<26 weeks) previously published¹⁶ for the years 2000–2001 (period I: before the publication of the Swiss recommendations) and the years 2003–2004 (period II: following the publication of the Swiss recommendations), a third time period consisting

of the years 2005–2009 (period III) was added. To examine the trend of CTC variation in survival rates, all live born preterm infants with a GA between 23 0/7 weeks and 31 6/7 weeks born in the entire 10-year study period were analysed. GA-specific survival rates of preterm infants born in 2000–2004 were compared with survival rates of those born in 2005–2009.

For more detailed analysis of CTC variability, we calculated centre-specific risk-adjusted survival rates in three different GA groups. Group A consisted of infants born at the limit of viability (23–25 completed weeks; infants born at 22 completed weeks were excluded because no centre reported any survivors at this GA); group A infants are subject to the Swiss recommendations and a certain CTC variability can be expected because interpretation of the guidelines may differ between centres. Group B consisted of more mature extremely preterm infants (26–28 completed weeks) in whom CTC outcome differences would be expected to become smaller. Finally, group C consisted of preterm infants with a GA of 29–31 completed weeks in whom survival rates are excellent and CTC outcome variability should no longer be significant. For these analyses, infants with severe or lethal malformations (ie, critical congenital heart disease (eg, hypoplastic left heart syndrome, transposition of the great arteries and Epstein's anomaly), severe central nervous system malformations (eg, anencephaly, holoprosencephaly and occipital myelomeningocele), lethal chromosomal anomalies (eg, trisomy 13, trisomy 18 and triploidy)) were excluded to eliminate any bias related to variability in referral patterns to high-risk obstetrical services.

Comparisons of proportions were performed using Fisher's exact test for small groups. Two-sided p values <0.05 were considered significant. To examine CTC outcome variability, centre-specific adjusted OR and CI for survival were calculated using a logistic regression model standardised for birth weight (in grams), GA (in days), sex and singleton/multiple birth. Adjustment for antenatal corticosteroids was not possible because this information was not collected in the early years of the study period. The adjusted OR compare survival rates of one centre with the average survival rates of all the other centres.

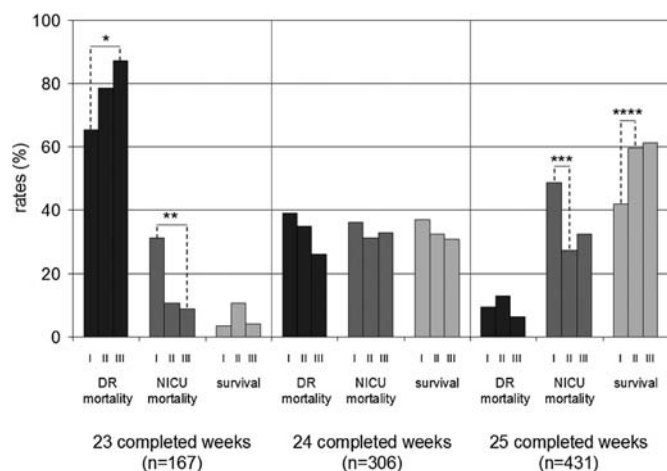


Figure 2 Trends for gestational age-specific mortality and survival rates over three time periods. Period I: 2000–2001, period II: 2003–2004 and period III: 2005–2009 (* $p=0.04$; ** $p=0.01$; *** $p=0.002$; **** $p=0.01$).

Statistical analyses were performed using Stat10 (StatCorp LP, College Station, Texas, USA). Graphs were created using GraphPad Prism 5 (GraphPad Software Inc, San Diego, California, USA).

Results

Trends in survival rates

Over the entire 10-year study period, 6532 preterm infants were born alive at a GA of less than 32 weeks in Switzerland, representing 0.8% of all live births.¹⁸ Details of the study population are shown in figure 1.

Survival rates of preterm infants with a GA of 23 completed weeks have remained unchanged over the 10-year study period at less than 10%. In the majority of these infants, life-sustaining therapies were withheld and death occurred in the delivery room. In fact, significantly more infants at 23 completed weeks died in the delivery room following primary non-intervention in period III than in period I (88% and 66%, respectively; $p=0.04$) (figure 2). At 24 completed weeks of gestation, survival rates also remained unchanged at 26%, 33% and 32% for time periods I, II and III, respectively (figure 2). The previously reported significant increase in survival rates of infants with a GA of 25 completed weeks after the publication of the Swiss recommendations for the care of infants born at the limit of viability from 42% in period I (2000–2001) to 60% in period II (2003–2004)¹⁶ was not followed by additional improvements, but remained constant over the next 5 years (period III: 2005–2009: 63%) (figure 2).

Centre-to-centre variations

CTC differences in survival rates of extremely preterm infants with at a GA of less than 26 completed weeks born alive in Switzerland between 2000 and 2004¹⁶ have persisted over the next 5 years (2005–2009). In addition, CTC outcome differences were not restricted to infants born at the limit of viability (23–25 completed weeks) but extended to more mature preterm infants (26–31 completed weeks) (figure 3).

The centre-specific adjusted ORs and 95% CI for survival in the three GA groups are shown in table 1. For group A infants (GA 23–25 completed weeks, $n=976$), three centres had significantly higher and three centres significantly lower adjusted ORs

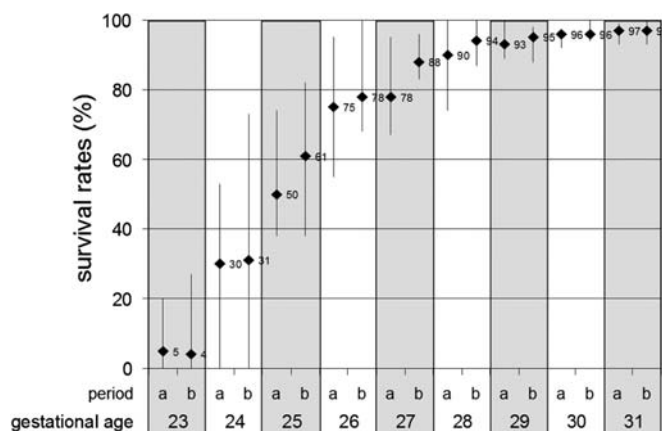


Figure 3 Unadjusted centre-to-centre variability of gestational age-specific survival rates in two time periods: (A) 2000–2004 and (B) 2005–2009 (black diamonds: average overall survival rate in Switzerland; vertical lines indicate range of survival rates observed).

Table 1 Centre-specific OR and 95% CI of survival among infants in three different gestational age groups in Switzerland over a 10-year period (2000–2009) standardised for gestational age, birth weight, single/multiple birth and sex; infants with lethal/severe malformations were excluded.

Centre	N	Gestational age group (completed weeks)		
		23–25 OR (95% CI) (n=976)	26–28 OR (95% CI) (n=1943)	29–31 OR (95% CI) (n=3399)
1	765	1.49 (0.99 to 2.25)	0.85 (0.57 to 1.25)	0.61 (0.35 to 1.09)
2	830	0.56 (0.33 to 0.94)*	0.78 (0.55 to 1.15)	0.98 (0.52 to 1.87)
3	1047	1.39 (0.95 to 2.03)	1.86 (1.23 to 2.81)†	1.86 (0.89 to 3.88)
4	566	2.57 (1.50 to 4.42)†	2.51 (1.36 to 4.65)†	1.66 (0.67 to 4.14)
5	466	0.47 (0.23 to 0.95)*	0.82 (0.51 to 1.34)	1.68 (0.61 to 4.64)
6	656	2.73 (1.72 to 4.34)†	4.26 (1.96 to 9.23)†	1.53 (0.67 to 3.54)
7	1301	0.24 (0.15 to 0.36)*	0.34 (0.26 to 0.46)*	0.61 (0.37 to 0.98)*
8	497	1.91 (1.13 to 3.24)†	2.20 (1.13 to 4.29)†	0.86 (0.39 to 1.88)
9	190	0.49 (0.19 to 1.28)	1.12 (0.43 to 2.90)	0.91 (0.28 to 2.95)

*Statistically significant lower survival rate.

†Statistically significant higher survival rate.

for survival compared with the rest of the country. For group B infants (GA of 26–28 weeks, $n=1943$), four centres had significantly higher adjusted ORs for survival and one centre had a significantly lower adjusted OR. Finally, in group C infants (GA of 29 0/7 to 31 6/7, $n=3399$), adjusted ORs for survival were no longer statistically different among eight centres but remained significantly lower in one centre. Interestingly, centre performances appear to be consistent across the three GA groups.

Discussion

We have previously reported changes in survival rates of extremely preterm infants in Switzerland.¹⁶ There were two main study findings: first, the publication of Swiss

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Table 2 Comparison of survival rates of extremely preterm infants with a gestational age between 22 and 25 completed weeks in Switzerland, the UK, Finland, the USA and Sweden (all are population-based, multicentre studies including inborns and outborns)

Reference	Switzerland				UK Trent		Finland		USA (NICHD)		Sweden
	16		Current study		20		19		5	4	2
	Overall	CTC range	Overall	CTC range							
Time period	2000 to 2004		2005 to 2009		1994 to 1999	2000 to 2005	1996 to 1997	1999 to 2000	1998 to 2003	2003 to 2007	2004 to 2007
Total population											
Live births, N	516		551		682	669	152	160	4446	4160	707
Survivors, N	180		192		174	236	57	75	2267	2077	497
Survivors, %	35%	16–53%	35%	20–53%	26%	35%	38%	47%	51%	50%	70%
22 weeks											
Live births, N	18		54		81	69	21	19	NA	421	51
Survivors, N	0		0		0	0	1	0	NA	25	5
Survivors, %	0%	0%	0%	0%	0%	0%	5%	0%	5%	6%	10%
23 weeks											
Live births, N	82		101		148	131	36	29	NA	871	101
Survivors, N	4		4		15	12	4	7	NA	226	53
Survivors, %	5%	0–20%	4%	0–27%	10%	9%	11%	24%	26%	26%	52%
24 weeks											
Live births, N	158		179		198	227	44	53	NA	1370	144
Survivors, N	47		55		40	82	18	25	NA	748	96
Survivors, %	30%	0–53%	31%	0–73%	20%	36%	41%	47%	56%	55%	67%
25 weeks											
Live births, N	258		217		255	242	51	59	NA	1498	205
Survivors, N	129		133		119	142	34	43	NA	1078	167
Survivors, %	50%	38–74%	61%	38–82%	47%	59%	67%	73%	75%	72%	81%

CTC, centre-to-centre; NICHD, National Institute of Child Health and Human Development; NA, not available.

recommendations for the care of infants born at the limit of viability was followed by increased survival rates without concomitant increases in short-term complication rates, and second, there were considerable CTC differences in survival rates despite the availability of national recommendations.

Trends in survival rates

The present study extended our previous investigations from 5 to 10 years and allowed us to follow-up on the trend in survival rates of borderline viable infants in Switzerland. Our finding that survival rates of preterm infants with a GA of less than 24 0/7 weeks remained low, and the majority of these infants had died in the delivery room following comfort care (figure 2) is consistent with the current Swiss recommendations.⁸ While survival at 22 completed weeks is exceptional in most NICUs, survival rates at 23 completed weeks have been reported in recent studies to range between 22% and 52%,^{12–14} rates that are much higher than the average 5% observed in Switzerland.

On a national level, following an increase between 2001–2002 and 2003–2004,¹⁶ we observed no further improvement in survival rates of infants with a GA between 24 0/7 weeks and 25 6/7 weeks. This is similar to recent observations from the Neonatal Research Network of the National Institute of Child Health and Human Development (NICHD) in the USA⁴⁵ and from Finland.¹⁹ Average survival rates of the most immature extremely low GA infants in Switzerland are remarkably similar to the experience reported by Field *et al* for the Trent health region,²⁰ but significantly lower than those observed in US, Finnish and Swedish NICUs (table 2).^{2–4,5,19}

Interestingly, some Swiss centres achieve survival rates that are as high as those reported from the US and Scandinavian countries. In Sweden, Fellman *et al* have shown that proactive

perinatal management can result in remarkably high survival rates among extremely preterm infants.² It is likely that some centres in Switzerland have adopted similar approaches at 24 and 25 completed weeks since survival rates are almost identical to those reported from Sweden. However, at 22 and 23 completed weeks, life-sustaining interventions are only rarely offered in Switzerland and survival rates in all Swiss centres remain well below the Swedish results (table 2).

Centre-to-centre variations

The extension of the dataset to a 10-year period (2000–2009), the exclusion of infants with severe or lethal malformations, and inclusion of more mature preterm infants (26–31 completed weeks) allowed us to gain further insight into CTC differences in survival rates.

We now show that CTC variations continued to persist over the next 5 years (figure 2), making it unlikely that a simple time lag in the implementation of new recommendations could have been responsible for lack of an effect on CTC variations. The differences were noted for delivery room and NICU mortality rates (data not shown). Because delivery room mortality of extremely preterm infants is most commonly related to primary non-intervention (ie, withholding of life-sustaining therapies) rather than the consequence of unsuccessful resuscitation, the centres are likely to differ in their attitudes towards active obstetrical interventions and initiation of provisional intensive care. Differences in NICU mortality rates, on the other hand, could either be related to illness severity or, alternatively, to different thresholds to limiting or withdrawing intensive care measures.

Contrary to our hypothesis, CTC outcome variations were not restricted to borderline viable preterm infants (table 1).

Statistically significant differences in survival rates were also observed for preterm infants with a GA between 26 and 28 completed weeks (adjusted ORs significantly higher in four centres, significantly lower in one centre) and even for preterm infants with a GA between 29 and 31 completed weeks (adjusted OR significantly lower in one centre). In addition, centre performances were consistent across the three GA strata and did not correlate with centre case loads. These observations suggest that factors other than baseline population demographics (which we adjusted for) or differences in the interpretation of national recommendations (which are restricted to the care of infants with GA<26 completed weeks) influence survival rates of extremely preterm infants in the individual centres.

Significant CTC outcome variations have been reported from other countries. Tommiska *et al* noted a twofold difference in neonatal mortality rates between secondary and tertiary level hospitals in Finland among 349 extremely low birth weight infants (birth weight <1000 g, GA at least 22 completed weeks) born in 1996/1997 (59% vs 32%, $p < 0.001$).²¹ When the same authors analysed a second cohort of extremely low birth weight infants born 3 years later (1999/2000), they found no improvement in mortality rates and a persistence of CTC differences.¹⁹ Kusuda *et al* found variations in medical interventions and clinical outcomes among 37 participating NICUs in Japan. While the average survival rate of 2145 very low birth weight infants born in 2003 was 89%, standardised survival rates varied between 70% and 100%.²² In a report on 2478 live born extremely low birth weight infants from the Neonatal Research Network of the National Institute of Child Health and Human Development (NICHD 1993/1994), Vohr *et al* found striking differences in centre outcomes after adjusting for demographics and antenatal interventions.²³ They suggested that variations in active resuscitation (5–28%) and in survival rates (51–72%) reflect in part differences in management styles. In Canada, Lee *et al.* evaluated outcomes of infants of 22 to 25 weeks' gestation in 12 hospitals of the Canadian NICU Network. They found that delivery room death rates ranged from 9% to 57% and neonatal survival rates ranged from 32% to 79%.²⁴

Limitations of the study

The present study is a large population-based analysis of temporal trends and CTC variations in survival rates of extremely preterm infants over a 10-year period in Switzerland. The study has several limitations. Although we have ascertained that all live born infants (including delivery room deaths) were included, there may have been borderline viable infants who died in delivery rooms of smaller hospitals. This number is likely to be small because antenatal referral of high-risk pregnancies is well established in Switzerland. Conclusions that can be drawn from our observation of significant CTC variations are limited because no information on illness severity, measures instituted during provisional intensive care and details on circumstances of delivery room and NICU deaths were available. Finally, complete information on long-term outcome of survivors is not yet available, and therefore a more comprehensive assessment of the impact of the observed trends and CTC variations is not possible.

Conclusions

In Switzerland, consistent with national recommendations for the care of infants born at the limit of viability published in 2002,⁸ active resuscitation of preterm infants with a GA <24 0/7 weeks is rarely attempted. After initial improvement

following the publication of the Swiss recommendations, survival rates of preterm infants with a GA of 25 completed weeks have since remained unchanged. Risk-adjusted CTC outcome differences have also continued to persist and are not restricted to borderline viable infants. Centre-specific factors other than differences in baseline demographics or in the interpretation of guidelines must be involved. There is an urgent need to gain further insights into these factors.

Contributors All of the listed authors have substantially contributed to this manuscript: conception and design, analysis and interpretation of data (TMB, MAS, MA), drafting the article (TMB, MAS) or revising it critically for important intellectual content (TMB, MAS, AW, P M-S, MA). All co-authors have approved of the final version submitted for publication.

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Competing interests None.

Ethics approval The study was approved by the National Ethics Committee and the National Expert Committee on Medical Confidentiality in Medical Research.

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